

**REMARKS**

Applicants respectfully request reconsideration and further examination in view of the following remarks.

Upon entry of this Amendment, claims 17-18, 21-23, and 34-44 will be pending in this application. By this Amendment, claims 1-16 and 24-33, which stand withdrawn from consideration as being directed to a nonelected invention, have been canceled without prejudice or disclaimer. Claim 19 has also been canceled without prejudice or disclaimer.

Claims 36-44 have been added. Claims 36-44 depend directly or indirectly from claims 17 and 18 and find support throughout the specification, including the original claims. Thus this Amendment does not introduce new matter. Applicants submit that new claims 36-44 do not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

Applicants respectfully request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims 17-18, 21-23, and 34-44 in condition for allowance, or in better form for appeal, should the Examiner dispute the patentability of the pending claims.

**Double Patenting Rejections**

The Office provisionally rejected claims 17 and 18 under 35 U.S.C. § 101 as allegedly claiming the same invention as that of claims 17 and 18 of copending application S.N. 09/501,787. (Paper No. 14, p.2.) Applicants have canceled claims 17 and 18 obviating this rejection.

The Office also provisionally rejected claims 19 and 21-23 under the judicially created doctrine of obviousness-type double patenting over claims 19 and 21-23 of copending application S.N. 09/501,787. (*Id.* at 3-4.) Applicants respectfully request that the Examiner hold this rejection in abeyance until allowable subject matter has been indicated.

**Rejections Under 35 U.S.C. § 112, First Paragraph**

The Office rejected claim 19 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art, at the time the application was filed, that the inventors had possession of the claimed invention. (Paper No. 14, pp. 4-5.) The Office also rejected claim 19 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. (Paper No. 14, pp. 6-7.) Although the Office acknowledges that the specification (see, e.g., Specification, Example 1) enables one of skill in the art

to make and use a hybrid fragment of tetanus toxin that combines a tetanus toxin fragment with the B-galactosidase ( $\beta$ -gal)<sup>1</sup> protein ("the *lacZ*-TTC construct"), the Office asserts that the specification does not reasonably enable the full scope of the claims. (*Id.* at 8.) Although applicants respectfully disagree with each of these 35 U.S.C. § 112, first paragraph rejections, in an effort to expedite prosecution, claim 19 has been canceled obviating these rejections.

**Rejection Under 35 U.S.C. § 103(a)**

The Examiner rejected claims 17-18, 21-23 and 34-35 under 35 U.S.C. § 103(a) as allegedly being obvious over Mueller, 1994 (Report, ARO-27890.1-LS, Order No. AD-A290 501, NTIS, p. 1-15) in view of Hohne-Zell et al., 1993 FEBS Letters, Vol. 336, No. 1, p. 175-180. (Paper No. 14, pp. 8-9.) Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the reference (or references when combined) must teach or suggest all elements of the claim. See M.P.E.P. § 2143.

The Office's obviousness rejection is improper for at least the reason that the references do not teach or suggest all elements of the claimed invention. Claims 17

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<sup>1</sup> The  $\beta$ -gal protein is encoded by the *lacZ* gene.  
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and 18 recite that the hybrid fragment includes a fragment B, or a fraction of fragment B having at least 11 amino acid residues. The remaining claims depend directly or indirectly from claims 17 or 18. Neither Mueller nor Hohne-Zell et al. teaches or suggests a hybrid tetanus toxin fragment that includes fragment B, or a fraction thereof having at least 11 amino acid residues. Indeed, in Paper No. 11, the Office acknowledged that "Mueller does not teach a hybrid fragment comprising fragment C of tetanus toxin and at least 11 amino acid residues of fragment B . . . ." (Paper No. 11, p. 10.)

In the present Office Action, the Office asserts:

Mueller teaches receptor mediated gene transfer in the central nervous system and "tetanus toxin is uniquely specific for uptake into neurons and enters the central nervous system from the circulation with the highest efficiency of any known protein." (e.g. p. 3). Tetanus toxin includes fragment B and C, and contains at least 11 amino acid residues of fragment [sic, fragment] B. Thus, Mueller implies the use of tetanus toxin that includes fragment B and fragment C for receptor mediated gene transfer in the central nervous system.

(Paper No. 14, p. 8.)

To the contrary, however, Mueller specifically teaches **excluding** fragment B from tetanus toxin fragments that were used in an attempt to achieve receptor mediated gene transfer. While the quoted language above from Mueller mentions the "tetanus toxin," the claims are directed to a **fragment** of tetanus toxin. Moreover, Mueller specifically discloses using only fragment C of the tetanus toxin. As shown in Mueller, proteolytic digestion of tetanus toxin produces two fragments: fragment C and fragment

B. (Mueller, p. 3, Figure 1.) Fragment C is not toxic, “yet it is sufficient for internalization and transport, and therefore could be safely utilized as a carrier molecule for neuron specific gene transfer *in vivo*.” (Mueller, p. 4.) Mueller “hypothesized that genes complexed to the **C-fragment** of tetanus toxin will be taken up efficiently and specifically by neurons.” (Mueller, p. 4; emphasis added.) Accordingly, Mueller set out to separate and purify fragment C from the remainder of the natural tetanus toxin (including fragment B). Specifically, Mueller prepared fragment C by digesting the tetanus toxin with the proteolytic enzyme, trypsin. (Mueller, p. 4.) The non-toxic fragment C obtained from the proteolytic digest was purified by either gel filtration or fast protein liquid chromatography. The purified fragment C was attached to polylysine, “which serves as a bridge for the non-covalent, electrostatic binding of negatively charged DNA.” (Mueller, p. 4, see *also*, Figure 3.) Mueller never mentions adding fragment B, or a fraction thereof, to the tetanus toxin fragment C. In fact, in the process of purifying fragment C, Mueller specifically teaches separating fragment C from fragment B and getting rid of the latter. Mueller, therefore, teaches away from the claimed invention.

Hohne-Zell et al. fail to remedy the deficiencies of Mueller. Hohne-Zell et al. generated and analyzed mutant tetanus toxin light chains to determine whether they could retain the ability of the wild type light chain to block the release of neurotransmitters. (Hohne-Zell et al., p. 176, first column.) As discussed in the specification, papain digestion of tetanus toxin produces fragment C and a portion

containing the light chain (fragment A) linked to fragment B by disulfide bonds.

(Specification, p. 2.) Therefore, Hohn-Zell et al. disclose using recombinant tetanus toxin light chains (i.e., fragment A)—not a hybrid fragment containing fragment C and fragment B.

The Office alleges that Hohne-Zell et al. teach that the putative zinc-binding domain contains the active site of the tetanus toxin light chain. (Paper No. 14, pp. 8-9.) Even if this characterization of Hohne-Zell et al. is accurate, the reference does not teach a hybrid fragment of tetanus toxin containing fragment C and fragment B (or a portion thereof), as recited in claims 17 and 18. Nor does it suggest such a fragment. Indeed, as discussed above, Mueller shows that a skilled artisan would be motivated to exclude fragment B from such a tetanus toxin fragment, because fragment C alone was believed to be sufficient for the transport properties of the natural tetanus toxin and because fragment C could be readily obtained by separating it from the remainder of the tetanus toxin (including fragment B) through known proteolytic digestion methods. Thus, the cited references, Mueller and Hohne-Zell et al., fail to teach or suggest all elements of the claimed invention. Accordingly, applicants respectfully request withdrawal of this 35 U.S.C. § 103 rejection.

### **CONCLUSION**

In view of the foregoing remarks, applicants respectfully request the examination on the merits of this application and the timely allowance of the pending claims.

Laurent COEN et al.  
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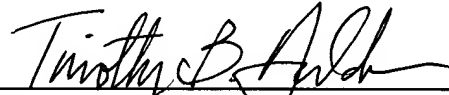
Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,  
GARRETT & DUNNER, L.L.P.

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By:

  
Timothy B. Donaldson  
Reg. No. 43,592

E-mail: [Timothy.Donaldson@finnegan.com](mailto:Timothy.Donaldson@finnegan.com)

Tel.: (202) 408-4058

Fax: (202) 408-4400